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Re: Intl. App. No.: PCT/US2004/010346
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Applicant: Applied Research Systems ARS Holding, NV
Title: "Inhibitors of Phosphodiesterases in Infertility"
Agent's File Reference: 05558.0011.00PC00
AMENDMENTS AND ARGUMENTS UNDER PCT ARTICLE 34

Dear Sirs:

Applicant submits the following amendments and arguments under PCT Article 34 in response to the written opinion of the International Searching Authority mailed October 26, 2004. Submitted herewith are the following: Chapter II Demand under PCT Article 31 (4 pages); PCT Fee Calculation Sheet (1 page); and replacement claim sheets 68-69.

AMENDMENTS

Multiple dependent claims 22-24 and 33 have been amended to remove dependency from claim 21. Replacement sheets 68 and 69 are enclosed.

ARGUMENTS

The International Searching Authority asserts that claims 1-66 fail to satisfy Article 33(1) as lacking novelty and inventive step based on reference D1: US2002/0065324. The International Searching Authority has characterized reference D1 as disclosing methods of inducing ovulation in a female host comprising the administration of a non-polypeptide cAMP level modulator to the female host, in particular specific administration of phosphodiesterase inhibitors, such as PDE4 inhibitors, prior to the luteal phase of the host's ovulatory cycle.

Applicant respectfully disagrees that the teachings of D1 anticipate the invention as claimed. D1 states that "the administration of nonpolypeptide cAMP level modulators have no therapeutic effect on follicular maturation and development during the ovulatory cycle." D1, ¶ 0063. D1 states that although PDE inhibitors may be used for ovulation induction, ovulation induction "does not include the preceding events in time during the ovulatory cycle of follicular maturation and development." D1, ¶ 0039.

Claims 1-20, 22-24, 33-34, and 42-60 relate to the use of a phosphodiesterase inhibiting enzyme for the stimulation of follicular maturation *in vivo*, as do claims 25-32, 35-36 and 38-41. Because D1 explicitly states the opposite: that inhibitors of phosphodiesterases do not enhance follicular growth *in vivo*, D1 cannot be said to anticipate claims 1-20, 22-24, 33-34, and 42-60 or the relevant portions of claims 25-32, 35-36, and 38-41.

Claim 21 relates to in vitro stimulation of an immature oocyte with a PDE inhibitor in an amount effective to cause oocyte maturation, as do claims 25-32, 35-36, and 38-41. D1 does not address maturation of immature oocytes *in vitro*. As described in paragraph [0109] of the instant specification as filed, oocytes may also be retrieved from the patient's antral (mature) follicles before they are ovulated and stimulated with PDE inhibitors. In contrast, D1 refers only to the treatment of the patient directly.

Claim 37 relates to a vial containing a single dose of a PDE 4 inhibitor along with FSH. D1 does not teach a vial containing a combination of PDE 4 inhibitor and FSH. D1 does not teach that PDE 4 inhibitor and FSH can be simultaneously administered. In D1 Example 2, the only example teaching the simultaneous administration of FSH and PDE inhibitor, the results showed "that increasing doses of PDE inhibitor failed to enhance the ability of a sub-optimal dose of FSH to prepare follicles to ovulate." Therefore, D1 teaches away from the claimed combination as non-functional. In Examples 3-9, the other examples in which FSH was provided, FSH administration was stopped prior to administration of the PDE inhibitor.

Claims 61-66 relate to a kit for the treatment of infertility using a PDE 4 inhibitor and FSH. D1 does not teach the use of a kit in the treatment of infertility.

CONCLUSION

Applicant respectfully requests consideration of these amendments and arguments in the preparation of an international preliminary examination report.

Respectfully submitted,

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20. A method of increasing follicle maturation comprising treating a female with a composition comprising a phosphodiesterase (PDE) inhibitor in an amount effective to stimulate follicular maturation.

21. A method of increasing oocyte maturation comprising treating an oocyte *in vitro* with a composition comprising a PDE inhibitor in an amount effective to cause oocyte maturation.

22. A method according to claim 20, wherein the composition comprises at least one PDE 4 inhibitor.

23. A method according to claim 20, wherein the composition comprises at least one PDE 4 inhibitor selected from the group consisting of Piclamilast, Roflumilast, Ariflo, Filaminast, Mesopram, D4418, Arofylline, and CL1044.

24. A method according to claim 20, wherein the composition comprises at least one PDE 4 inhibitor and one other PDE inhibitor selected from the group consisting of a PDE 1 inhibitor, a PDE 7 inhibitor, a PDE 9 inhibitor, a PDE 10 inhibitor, and a PDE 11 inhibitor.

25. A method according to claim 20 or 21, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

26. A method according to claim 22, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

27. A method according to claim 23, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

28. A method according to claim 24, wherein the method further comprises treatment with at least one gonadotropin selected from the group consisting of FSH, luteinizing hormone, and chorionic gonadotropin.

29. A method according to claim 20 or 21, wherein the method further comprises treatment with FSH.

30. A method according to claim 20 or 21, wherein the method further comprises administering FSH and at least one non-FSH gonadotropin hormone.

31. A method according to claim 30, wherein the non-FSH gonadotropin hormone is luteinizing hormone.

32. A method according to claim 30, wherein the non-FSH gonadotropin hormone is chorionic gonadotropin.

33. A method according to claim 20, wherein the method comprises administering a stimulator, agonist or adjuvant of FSH alone in combination with a PDE 4 inhibitor.

34. A method according to claim 33, wherein the stimulator of FSH is selected from the group consisting of Letrozole, Anastrozole, and Vorozole.

35. A method according to claim 25, wherein the PDE inhibitor and the gonadotropin hormone are administered concurrently.

36. A method according to claim 25, wherein the PDE 4 inhibitor and FSH are contained in a single vial as a mixture.

37. A vial containing a single dose of a mixture of PDE 4 inhibitor and FSH.

38. A method according to claim 25, wherein the PDE inhibitor is administered prior to the gonadotropin hormone treatment.